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THOMSON HEALTHCARE

ISBN: 1-56363-330-2

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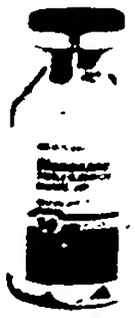


30 units per vial
Also available in 15 units per vial.

Blenoxane®
(sterile bleomycin sulfate, USP)

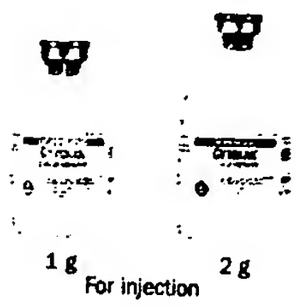
BRISTOL-MYERS SQUIBB ONCOLOGY P. 1037

25 mg 50 mg

Cytoxan®
(cyclophosphamide tablets, USP)

BRISTOL-MYERS SQUIBB ONCOLOGY P. 1037

00 mg 200 mg 500 mg

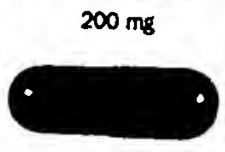


1 g 2 g
For injection

Lyophilized Cytoxan®
clophosphamide for injection, USP)

BRISTOL-MYERS SQUIBB ONCOLOGY P. 1039

200 mg

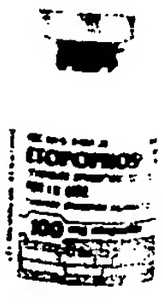


300 mg

400 mg

Droxia™
(hydroxyurea capsules, USP)

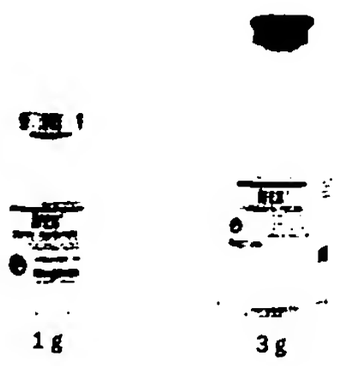
RISTOL-MYERS SQUIBB ONCOLOGY P. 1041



100 mg
Single-dose vial

Etopophos®
ioside phosphate) for Injection

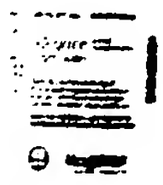
RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1044



1 g 3 g

Ifex®
(ifosfamide for injection)

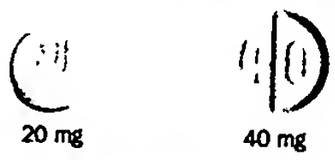
RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1047



40 mg/mL

Megace® Oral Suspension
(megestrol acetate)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1048



20 mg 40 mg

Megace®
(megestrol acetate tablets, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1049

1-gm Multi-dose vial

Mesnex®
(mesna) Injection

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1050

40 mg
Also available in 5 mg and 20 mg

Mutamycin®
(mitomycin for injection, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1052

50 mg 150 mg

450 mg

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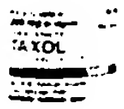
(carboplatin for injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1055

50 mg 100 mg

Platinol®-AQ
(cisplatin injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1059



300 mg Multi-dose vial
Also available in 30 mg, 100 mg Multi-dose vials

TAXOL®
(paclitaxel) Injection
6 mg/mL

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1068

100 mg
Also available in 150 mg, 500 mg, 1 g

VePesid®
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RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1068

50 mg

VePesid®
(etoposide) Capsules

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1070

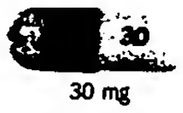
100 mg
Also available in 200 mg tablets for once a day dosing

Videx®
(didanosine)
Chewable/Dispersible Buffered Tablets

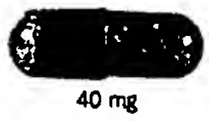
RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1072

15 mg

20 mg



30 mg



40 mg

Zerit®
(stavudine) Capsules

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 1072

1 mg/mL
200 mL

Zerit®
(stavudine) for Oral Solution

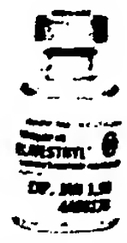
BTG PHARMACEUTICALS

C-III BTG PHARMACEUTICALS P. 1076

2.5 mg tablets

Oxandrin®
(oxandrolone tablets, USP)

RX BTG PHARMACEUTICALS P. 1075



200 mg/mL
5 mL multiple dose vial

200 mg/mL
1 mL unimatic single dose syringe

Delatestryl®
(testosterone enanthate Injection, USP)

CARNRICK

RX CARNRICK P. 1077

Midrin®
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65 mg / 100 mg / 325 mg

RX CARNRICK P. 1078

375 mg

500 mg

Naprelan®
(naproxen sodium controlled-release tablets)

RX CARNRICK P. 1080

400 mg

Skelaxin®
(metaxalone)

CELGENE

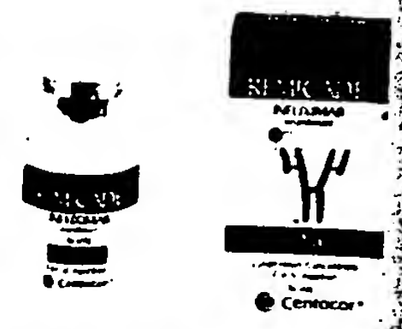
RX CELGENE CORPORATION P. 1

50 mg

THALOMID®
(thalidomide) Capsules

CENTOCOR, INC.

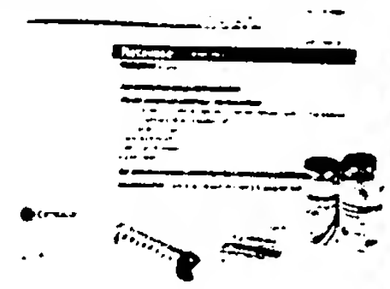
RX CENTOCOR, INC. P. 1



100 mg
Lyophilized Concentrate For IV Injection

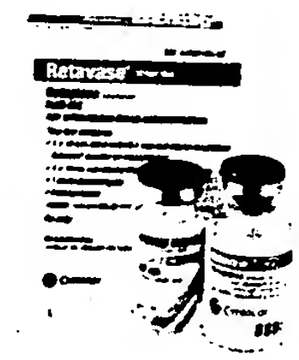
Remicade®
(infliximab recombinant)

RX CENTOCOR, INC. P. 1



Retavase® Full-Kit
(reteplase recombinant)

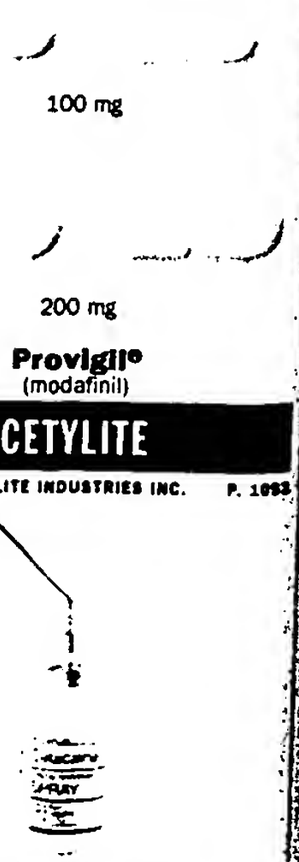
RX CENTOCOR, INC. P. 1



Retavase® Half-Kit
(reteplase recombinant)

CEPHALON, INC.

C-IV CEPHALON, INC. P. 1



100 mg

200 mg

Provigil®
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CETYLITE

RX CETYLITE INDUSTRIES INC. P. 1

Topical Anesthetic Spray

Cetacaine®
(benzocaine, butamben & tetracaine HCl)

REST AVAILABLE COPY

I understand that THALOMID® (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.
I have read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)". I understand the contents, including other possible health problems from THALOMID® (thalidomide), so-called "side effects". I know that I cannot donate blood or semen while taking THALOMID® (thalidomide).
My doctor has answered any questions I have asked.
I understand that I must participate in a survey and patient registry while I am on THALOMID® (thalidomide), which will require completing additional forms.

...mation has been read aloud to me in the language of my choice. I understand that if I do not follow ...doctor's instructions, I will not be able to receive THALOMID® (thalidomide). I now authorize my doctor to begin my treatment with THALOMID® (thalidomide).

Social Security No. (Only last six digits required) | Date of Birth (mo./day/yr.)

...ent/ Signature | Date (mo./day/yr.)

...ly explained to the patient the nature, purpose, risks of the treatment described above, especially risks to women of childbearing potential. I ...the patient if she/he has any questions regarding this treatment with THALOMID® (thalidomide). I have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed. In addition, I will comply with all of my obligations and responsibilities as a prescriber registered under the THALOMID® restricted distribution program.

...Name | DEA No.

...Signature | Date (mo./day/yr.)

...DES
...M. 1986. Teratogenicity. Cassarett and Doull's ...The Basic Science of Poisons. Third Edition. ...220. New York: MacMillan Publishing Co.
...MW and Newman CG. 1992. J. Med. Genet. ...723.
...EP, Kaplan G, Miranda A, *et al.* 1993. J. Infect. ...408–414.
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...anguilon J, Ramanujam K, *et al.* 1971. Bull. ...15–782.
...nd Convit J. 1969. Intl. J. Leprosy. 37:135–
...R. 1971. Lepr. Rev. 42:26–42.
...data, on file at Celgene.
...CG
...Product Identification Guide, page 310

...ERGENCY telephone numbers, ...the Manufacturers' Index.

Centocor, Inc.
200 GREAT VALLEY PARKWAY
MALVERN, PA 19355

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Ph: (800) 457-6399
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REMICADE®
INFLIXIMAB
recombinant
For IV Injection

℞

DESCRIPTION

REMICADE® (infliximab) is a chimeric $IgG1_\kappa$ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.
REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate and 6.1 mg dibasic sodium phosphate. No preservatives are present.

CLINICAL PHARMACOLOGY

General
Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[1–4] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* by complement or effector cells.[2] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils,[3] B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and, when administered after disease onset, allows eroded joints to heal.
Pharmacodynamics
Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients[5] and the stools of Crohn's disease patients[6] and correlate with elevated disease activity. In Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon γ.[4] In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [interleukin 8 (IL-8) and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3].[4] After treatment with REMICADE, patients with Crohn's disease or rheumatoid arthritis exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients.
Pharmacokinetics
Single intravenous infusions of 1 to 20 mg/kg showed a predictable and linear relationship between the dose administered and the maximum serum concentration and area under the concentration-time curve. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Median pharmacokinetic results for the recommended doses of 3 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the terminal half-life of infliximab is 8.0 to 9.5 days.
Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks in fistulizing Crohn's disease and rheumatoid arthritis patients resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals in rheumatoid arthritis patients or patients with moderate or severe Crohn's disease retreated with 4 infusions of 10 mg/kg REMICADE at 8-week intervals. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age or weight. It is not known if there are differences in clearance or volume of distribution between gender subgroups or in patients with marked impairment of hepatic or renal function.

CLINICAL STUDIES
Rheumatoid Arthritis
The safety and efficacy of REMICADE when given in conjunction with methotrexate (MTX) were assessed in a multicenter, randomized, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT). The median age of patients enrolled was 54 years, with a median duration of disease of 8.4 years and a median number of swollen and tender joints of 20 and 31 respectively. All patients were to have received MTX for ≥ 6 months and be on a stable dose ≥ 12.5 mg/week for 4 weeks prior to study. All REMICADE and placebo groups continued their stable dose of MTX and folic acid.
In addition to MTX, patients received placebo, 3 mg/kg or 10 mg/kg of REMICADE by intravenous infusion at weeks 0, 2 and 6 followed by additional infusions every four or eight weeks thereafter. Concurrent use of stable doses of oral corticosteroids (10 mg/day) and/or nonsteroidal anti-inflammatory drugs was also permitted. The primary endpoint was the proportion of patients at week 30 who attained an improvement in signs and symptoms as measured by the American College of Rheumatology criteria, (ACR 20). An ACR 20 response is defined as at least a 20% improvement in both tender and swollen joint counts and in 3 of the following 5 criteria: physician global assessment, patient global assessment, functional/disability measure, visual analog pain scale and erythrocyte sedimentation rate (ESR) or CRP.
At week 30, 43/86 (50%) of patients treated every 8 weeks with 3 mg/kg of REMICADE plus MTX attained an ACR 20 compared with 18/88 (20%) of patients treated with placebo plus MTX ($p<0.001$). Higher doses and/or more frequent administrations did not result in higher response rates. Results are shown in Figure 1.

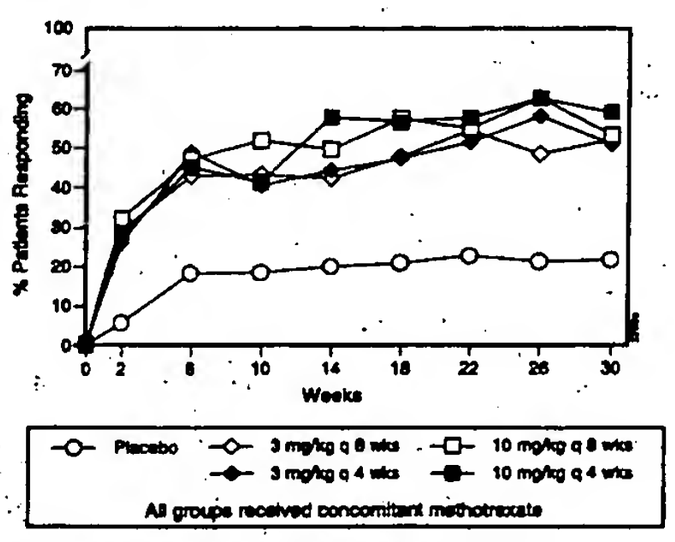

Figure 1. Percentage of Patients who Achieved an ACR 20.

At week 30, the ACR 50 response was 27% for patients treated with 3 mg/kg REMICADE (infliximab) every 8 weeks plus MTX, compared to 5% for patients treated with placebo plus MTX ($p<0.001$). The ACR 70 response was 8% for patients treated with 3 mg/kg REMICADE every 8 weeks plus MTX and 0% for patients treated with placebo plus MTX. Patients receiving 3 mg/kg REMICADE every 8 weeks demonstrated superior improvement in all ACR response components except HAQ compared to patients treated with placebo plus MTX (Table 1). Data on use of REMICADE without concurrent MTX are limited (see *PRECAUTIONS, Immunogenicity*).[7,8]
[See table 1 at top of next page]
Active Crohn's Disease
The safety and efficacy of REMICADE were assessed in a randomized, double-blind, placebo-controlled dose ranging study of 108 patients with moderate to severe active Crohn's disease[9] [Crohn's Disease Activity Index (CDAI) ≥220≤400]. All patients had experienced an inadequate response to prior conventional therapies, including corticosteroids (60% of patients), 5-aminosalicylates (5-ASA) (60%) and/or 6-mercaptopurine/azathioprine (6-MP/AZA) (37%). Concurrent use of stable dose regimens of corticosteroids, 5-ASA, 6-MP and/or AZA was permitted and 92% of patients continued to receive at least one of these medications.
The study was divided into three phases. In the first phase, patients were randomized to receive a single intravenous

Continued on next page

Remicade—Cont.

(IV) dose of placebo, 5, 10 or 20 mg/kg of REMICADE. The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥70 points from baseline at the 4-week evaluation and without an increase in Crohn's disease medications or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients who were in clinical remission at week 4 (CDAI <150), and clinical response over time.

At week 4, four of twenty-five (16%) of the placebo patients achieved a clinical response vs. twenty-two of twenty-seven (82%) of the patients receiving 5 mg/kg REMICADE ($p < 0.001$, two-sided, Fisher's Exact test). One of twenty-five (4%) placebo patients and thirteen of twenty-seven (48%) patients receiving 5 mg/kg REMICADE achieved a CDAI <150 at week 4. The maximum response to any dose of REMICADE was observed within 2 to 4 weeks. The proportion of patients responding gradually diminished over the 12 weeks of the evaluation period. There was no evidence of a dose response; doses higher than 5 mg/kg did not result in a greater proportion of responders. Results are shown in Figure 2.

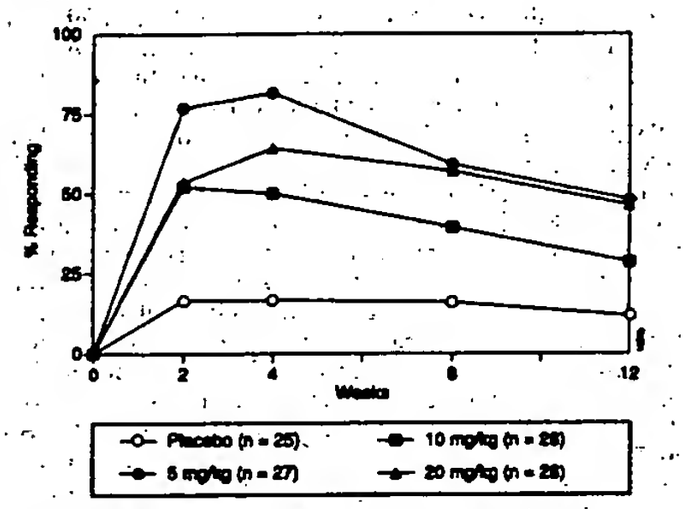

Figure 2. Response (≥70 point decrease in CDAI) to a Single IV REMICADE or Placebo Dose.

During the 12-week period following infusion, patients treated with REMICADE compared to placebo demonstrated improvement in outcomes measured by the Inflammatory Bowel Disease Questionnaire.

In the second phase, 29 patients who did not respond to the single dose of 5, 10 or 20 mg/kg of REMICADE entered the open label phase and received a single 10 mg/kg dose of REMICADE 4 weeks after the initial dose. Ten of twenty-nine (34%) patients experienced a response 4 weeks after receiving the second dose.

Patients who remained in clinical response at week 8 during the first or second phase were eligible for the retreatment phase. Seventy-three patients were re-randomized at week 12 to receive 4 infusions of placebo or 10 mg/kg REMICADE at 8-week intervals (weeks 12, 20, 28, 36) and were followed to week 48. In the limited data set available, no significant differences were observed between the REMICADE and placebo re-treated groups.

Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in a randomized, double-blind, placebo controlled study of 94 patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration.[10] Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, MTX, 6-MP and/or AZA was permitted, and 83% of patients continued to receive at least one of these medications. Fifty-two (55%) had multiple cutaneously draining fistulas, 90% of patients had fistula(s) in the perianal area and 10% had abdominal fistula(s).

Patients received 3 doses of placebo, 5 or 10 mg/kg REMICADE at weeks 0, 2 and 6 and were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistula(s) draining upon gentle compression, on at least two consecutive visits, without an increase in medication or surgery for Crohn's disease.

Eight of thirty-one (26%) patients in the placebo arm achieved a clinical response vs. twenty-one of the thirty-one (68%) patients in the 5 mg/kg REMICADE arm ($p = 0.002$, two-sided, Fisher's Exact test). Eighteen of thirty-two (56%) patients in the 10 mg/kg arm achieved a clinical response. The median time to onset of response in the REMICADE-treated group was 2 weeks. The median duration of response was 12 weeks; after 22 weeks there was no difference between either dose of REMICADE and placebo in the proportion of patients in response (Figure 3). New fistula(s) developed in approximately 15% of both REMICADE and placebo-treated patients.

[See figure 3 in next column]

Seven of sixty (12%) evaluable REMICADE-treated patients, compared to one of thirty-one (3.5%) placebo-treated patients, developed an abscess in the area of fistulas between 8 and 16 weeks after the last infusion of REMICADE. Six of the REMICADE patients who developed an abscess had experienced a clinical response (see *ADVERSE REACTIONS, Infections*).

Table 1

MEDIAN VALUES AT BASELINE & WEEK 30 FOR ACR COMPONENTS

	Placebo + MTX		3 mg/kg q 8 REMICADE
Parameter	Baseline	30 weeks	Baseline
No. of Tender Joints	24	16	32
No. of Swollen Joints	19	13	19
Pain[a]	6.7	5.9	7.0
Physician's Global Assessment[a]	6.5	5.0	6.1
Patient's Global Assessment[a]	6.2	5.5	6.6
Disability Index (HAQ)[b]	1.8	1.5	1.8
CRP (mg/dL)	3.0	2.3	3.1
ESR (mm/hr)	39	35	40

[a] Visual Analog Scale (0=best, 10=worst)

[b] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, hygiene, reach, grip, and activities

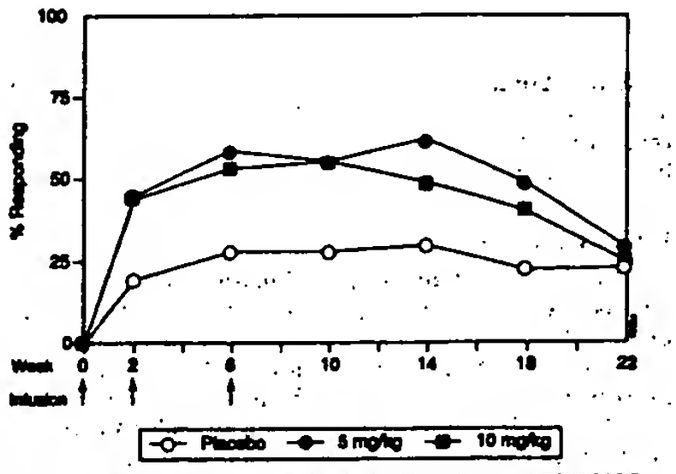

Figure 3. Response (fistula(s) closure) with Three Doses of REMICADE (infliximab) or Placebo.

Dose regimens other than dosing at weeks 0, 2 and 6 have not been studied. Studies have not been done to assess the effects of REMICADE on healing of the internal fistular canal, on closure of non-cutaneously draining fistulas (e.g., entero-entero), or on cutaneously draining fistulas in locations other than perianal and periabdominal.

INDICATIONS AND USAGE

Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for the reduction in signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate.

Crohn's Disease

REMICADE is indicated for the reduction in signs and symptoms of Crohn's disease in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

The safety and efficacy of therapy continued beyond a single dose have not been established (see *DOSAGE AND ADMINISTRATION*).

REMICADE is indicated for the reduction in the number of draining enterocutaneous fistulae in patients with fistulizing Crohn's disease.

The safety and efficacy of therapy continued beyond three doses have not been studied (see *DOSAGE AND ADMINISTRATION*).

CONTRAINDICATIONS

REMICADE should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS

RISK OF INFECTIONS

SERIOUS INFECTIONS, INCLUDING SEPSIS AND FATAL INFECTIONS, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH REMICADE SHOULD BE MONITORED CLOSELY. IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*).

Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infliximab infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of REMICADE, and possible loss of drug efficacy. REMICADE should be discontinued for severe reactions. [illegible] the treatment of hypersensitivity reactions (e.g., phen, antihistamines, corticosteroids and/or [illegible] should be available for immediate use in the [illegible] action (see *ADVERSE REACTIONS, Infusion-[illegible]tions*).

PRECAUTIONS

Autoimmunity

Treatment with REMICADE may result in the [illegible] autoantibodies and, rarely, in the development [illegible] like syndrome. If a patient develops symptoms [illegible] a lupus-like syndrome following treatment [illegible] CADE, treatment should be discontinued (see [illegible] *REACTIONS, Autoantibodies/Lupus-like Syn[illegible]*

Malignancy

Patients with long duration of Crohn's disease [illegible] toid arthritis and chronic exposure to immuno[illegible] therapies are more prone to develop lymphoma [illegible] *VERSE REACTIONS, Malignancies/Lympho[illegible] Disease*). The impact of treatment with REMI[illegible] these phenomena is unknown.

Immunogenicity

Treatment with REMICADE can be associated [illegible] velopment of antibodies to infliximab (also referr[illegible] man antichimeric antibodies, HACA). One hun[illegible] four of the 199 Crohn's disease patients treated [illegible] CADE were evaluated for the development of [illegible] specific antibodies; 18 (13%) were antibody-p[illegible] majority at low titer, <1:20). Patients who were [illegible] positive were more likely to experience an infusi[illegible] (see *ADVERSE REACTIONS, Infusion-related*). Antibody development was lower among rheumat[illegible] tis and Crohn's disease patients receiving immu[illegible] sant therapies such as 6-MP, AZA or MTX. With [illegible] dosing of REMICADE, serum concentrations of [illegible] were higher in rheumatoid arthritis patients who [illegible] concomitant MTX. There are limited data availa[illegible] development of antibodies to infliximab in patie[illegible] ing long-term treatment with REMICADE. Becau[illegible] nogenicity analyses are product-specific, comparis[illegible] body rates to those from other products is not a[illegible]

Vaccinations

No data are available on the response to vaccin[illegible] the secondary transmission of infection by live [illegible] patients receiving anti-TNF therapy. It is rec[illegible] that live vaccines not be given concurrently.

Drug Interactions

Specific drug interaction studies, including [illegible] with MTX, have not been conducted. The majo[illegible] tients in rheumatoid arthritis or Crohn's disease [illegible] als received one or more concomitant medication[illegible] matoid arthritis, concomitant medications [illegible] were nonsteroidal anti-inflammatory agents, folic [illegible] ticosteroids and/or narcotics. Concomitant Crohn's [illegible] medications were antibiotics, antivirals, corticos[illegible] 6-MP/AZA and aminosalicylates. Patients with Cr[illegible] ease who received immunosuppressants tended to [illegible] ence fewer infusion reactions compared to patie[illegible] immunosuppressants (see *PRECAUTIONS, Immun[illegible] ity* and *ADVERSE REACTIONS, Infusion-relat[illegible] tions*).

Carcinogenesis, Mutagenesis and Impairment of Fe[illegible]

Long-term studies in animals have not been perfo[illegible] evaluate the carcinogenic potential. No clastogenic [illegible] genic effects of infliximab were observed in the [illegible] mouse micronucleus test or the *Salmonella-Escheric[illegible]* (Ames) assay, respectively. Chromosomal aberrati[illegible] not observed in an assay performed using human [illegible] cytes. It is not known whether infliximab can impa[illegible] ity in humans. No impairment of fertility was obse[illegible] fertility and general reproduction toxicity study co[illegible] in mice using an analogous antibody that selectiv[illegible] its the functional activity of mouse TNFα.

Pregnancy Category C

Since infliximab does not cross-react with TNFα [illegible] other than humans and chimpanzees, animal repro[illegible] studies have not been conducted with REMICAD[illegible] imab). It is not known whether REMICADE can ca[illegible] harm when administered to a pregnant woman or c[illegible] reproduction capacity while infliximab is present [illegible] serum (see *CLINICAL PHARMACOLOGY, Pharmac[illegible] ics*). REMICADE should be given to a pregnant wom[illegible] if clearly needed. No evidence of maternal toxicity, [illegible] toxicity or teratogenicity was observed in a develo[illegible]

...city study conducted in mice using an analogous anti-...y that selectively inhibits the functional activity of ...se TNFα.

...ing Mothers

...s not known whether infliximab is excreted in human ...k or absorbed systemically after ingestion. Because ...ny drugs and immunoglobulins are excreted in human ...k, and because of the potential for adverse reactions in ...ing infants from REMICADE, a decision should be ...e whether to discontinue nursing or to discontinue the ...g, taking into account the importance of the drug to the ...er.

...atric Use

...ty and effectiveness of REMICADE in patients with ju-...le rheumatoid arthritis and in pediatric patients with ...n's disease have not been established.

...atric Use

...e ATTRACT study, no overall differences were observed ...ffectiveness or safety in the 72 patients aged 65 or older ...pared to younger patients. In Crohn's disease studies, ...e were insufficient numbers of patients aged 65 or older ...etermine whether they respond differently from patients ...d 18 to 65. Because there is a higher incidence of infec-...s in the elderly population in general, caution should be ...d in treating the elderly (see *ADVERSE REACTIONS*, ...ctions).

...VERSE REACTIONS

...otal of 771 patients were treated with REMICADE in ...ical trials. In both rheumatoid arthritis and Crohn's dis-... trials, approximately 5% of patients discontinued ...MICADE because of adverse experiences. The most com-... reasons for discontinuation of treatment were dyspnea, ...caria and headache.

...sion-related Reactions

...e infusion reactions

...infusion reaction was defined as any adverse event oc-...ing during the infusion or within 1 to 2 hours after the ...sion. Seventeen percent of REMICADE-treated patients ...clinical trials experienced an infusion reaction com-...d to 7% of placebo-treated patients. Among the 3284 ...ICADE infusions, 4% were accompanied by nonspecific ...ptoms such as fever or chills, 1% were accompanied by ...itus or urticaria, 1% were accompanied by cardiopulmo-... reactions (primarily chest pain, hypotension, hyper-...n or dyspnea), and 0.1% were accompanied by com-... symptoms of pruritus/urticaria and cardiopulmonary ...ions. Less than 2% of patients discontinued REMI-...E because of infusion reactions, and all patients recov-...d with treatment and/or discontinuation of infusion. ...ICADE infusions beyond the initial infusion in rheu-...d arthritis patients were not associated with a higher ...nce of reactions.

...nts with Crohn's disease who became positive for anti-... to infliximab were more likely to develop infusion re-...s than were those who were negative (36% vs. 11% ...ctively). Use of concomitant immunosuppressant ...s appeared to reduce the frequency of antibodies to in-...ab and infusion reactions (see *PRECAUTIONS, Im-...genicity* and *Drug Interactions*).

...ions following readministration

...clinical trial of forty patients with Crohn's disease re-...d with infliximab following a 2 to 4 year period with-... infliximab treatment, 10 patients experienced adverse ... manifesting 3 to 12 days following infusion of which ...re considered serious. Signs and symptoms included ...gia and/or arthralgia with fever and/or rash, with some ...nts also experiencing pruritus, facial, hand or lip ..., dysphagia, urticaria, sore throat, and headache. Pa-...s experiencing these adverse events had not experi-...d infusion-related adverse events associated with their ... infliximab therapy. Of the 40 patients enrolled, these ...e events occurred in 9 of 23 (39%) who had received ... formulation which is no longer in use and 1 of 17 (6%) ...received lyophilized formulation. The clinical data are ...dequate to determine if occurrence of these reactions is ...to differences in formulation. Patients' signs and symp-... improved substantially or resolved with treatment in ...ases. There are insufficient data on the incidence of ... events after drug-free intervals of less than 2 years. ...ver, these events have been observed infrequently in ... trials and post-marketing surveillance at intervals ... than 1 year.

...ons

...MICADE clinical trials, infections were reported by ...REMICADE-treated patients (average of 27 weeks of ...up) and by 16% of placebo-treated patients (average ... weeks of follow-up). The infections most frequently re-...d were upper respiratory tract infections (including, si-..., pharyngitis, and bronchitis) and urinary tract infec-... No increased risk of serious infections or sepsis has ...observed with Remicade compared to placebo. Among ...ICADE-treated patients, these serious infections in-...d pneumonia, cellulitis, pyelonephritis and sepsis. In ...TRACT study, one patient died with disseminated tu-...is and one died with disseminated coccidioidomyco-... The relationship to REMICADE is unknown (see ...NINGS, *Risk of Infections*). Twelve percent of patients ...tulizing Crohn's disease developed a new abscess 8 ... weeks after the last infusion of REMICADE (see ...ICAL STUDIES, *Fistulizing Crohn's Disease*).

...tibodies/Lupus-like Syndrome

...ts were tested for autoantibodies at multiple time ... In the rheumatoid arthritis ATTRACT study, 23% of

Table 2

ADVERSE EVENTS IN RHEUMATOID ARTHRITIS AND CROHN'S DISEASE TRIALS

	RHEUMATOID ARTHRITIS		CROHN'S DISEASE	
	Placebo (n=133)	REMICADE (infliximab) (n=555)	Placebo (n=56)	REMICADE (n=199)
Avg. weeks of follow-up	22.3	26.9	14.7	27.0
Respiratory				
Upper respiratory infection	13%	20%	9%	16%
Coughing	5%	10%	0%	5%
Sinusitis	3%	9%	2%	5%
Rhinitis	4%	8%	4%	6%
Pharyngitis	5%	8%	5%	9%
Bronchitis	2%	4%	2%	7%
Gastrointestinal				
Nausea	17%	14%	4%	17%
Abdominal Pain	7%	8%	4%	12%
Vomiting	10%	5%	0%	9%
Other				
Headache	10%	20%	21%	23%
Rash	4%	9%	5%	6%
Fatigue	5%	6%	5%	11%
Fever	4%	6%	7%	10%
Back pain	2%	6%	4%	5%
Pain	4%	6%	5%	9%
Urinary tract infection	3%	6%	4%	3%
Pruritus	0%	5%	2%	5%
Moniliasis	2%	3%	0%	5%

REMICADE-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared to 6% of placebo-treated patients. Anti-dsDNA antibodies developed in approximately 4% of REMICADE-treated patients, compared to none of the placebo-treated patients. No association was seen between REMICADE dose/schedule and development of ANA or anti-dsDNA.

Of Crohn's disease patients treated with REMICADE who were evaluated for antinuclear antibodies (ANA), 34% developed ANA between screening and last evaluation. Anti-dsDNA antibodies developed in approximately 9% of Crohn's disease patients treated with REMICADE. The development of anti-dsDNA antibodies was not related to either the dose or duration of REMICADE treatment. However, baseline therapy with an immunosuppressant in Crohn's disease patients was associated with reduced development of anti-dsDNA antibodies (3% compared to 21% in patients not receiving any immunosuppressant). Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA antibodies if they were ANA-positive at study entry.

Three patients developed clinical symptoms consistent with a lupus-like syndrome, two with rheumatoid arthritis and one with Crohn's disease. All three patients improved following discontinuation of therapy and appropriate medical treatment (see *PRECAUTIONS, Autoimmunity*).

Malignancies/Lymphoproliferative Disease

Five new and 2 recurrent malignancies were observed in 6 of 771 patients treated with REMICADE for up to 36 weeks in clinical trials. These were non-Hodgkin's B-cell lymphoma, breast cancer, melanoma, squamous cell cancer of the skin, and basal cell cancer. There are insufficient data to determine whether Remicade contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied [11,12] (see *PRECAUTIONS, Malignancy*).

Other Adverse Reactions

Adverse events occurring at a frequency of at least 5% in trials in patients with rheumatoid arthritis or Crohn's disease are shown in Table 2. Patients with Crohn's disease who were treated with REMICADE were more likely than patients with rheumatoid arthritis to experience adverse events associated with gastrointestinal symptoms.

[See table 2 above]

Serious adverse events by body system that occurred in all patients treated with REMICADE at frequencies <2% are as follows:

Body as a whole: abdominal hernia, chest pain, fall, pain

Blood: splenic infarction, splenomegaly

Cardiovascular: hypertension, hypotension, syncope

Central & Peripheral Nervous: dizziness, headache, upper motor neuron lesion

Collagen: lupus erythematosus syndrome, rheumatoid nodules

Ear and Hearing: ceruminosis

Gastrointestinal: abdominal pain, Crohn's disease, diarrhea, gastric ulcer, intestinal obstruction, intestinal perforation, intestinal stenosis, nausea, pancreatitis, proctalgia, vomiting

Heart Rate and Rhythm: palpitation, tachycardia

Liver and Biliary: cholecystitis

Metabolic and Nutritional: dehydration, pancreatic insufficiency, weight decrease

Musculoskeletal: arthropathy, back pain, bone fracture, myalgia, tendon disorder, tendon injury

Myo-, Endo-, Pericardial and Coronary Valve: cardiac failure, myocardial ischemia

Neoplasms: lymphoma

Platelet, Bleeding and Clotting: thrombocytopenia

Psychiatric: anxiety, confusion, delirium, depression, somnolence, suicide attempt

Red Blood Cell: anemia

Resistance Mechanism: abscess, cellulitis, fever, infection bacterial, sepsis

Respiratory: adult respiratory distress syndrome, bronchitis, coughing, dyspnea, pleurisy, pneumonia, pulmonary infiltration, respiratory insufficiency

Skin and Appendages: furunculosis, rash, increased sweating

Urinary: azotemia, dysuria, hydronephrosis, kidney infarction, renal failure, ureteral obstruction

Vascular (Extracardiac): brain infarction, pulmonary embolism, thrombophlebitis deep

White cell and Reticuloendothelial: leukopenia, lymphadenopathy

A greater proportion of patients enrolled into the ATTRACT trial who received REMICADE plus MTX experienced mild, transient elevations (<2 times the upper limit of normal) in AST or ALT (37% each) compared to patients treated with placebo plus MTX (AST: 24%, ALT: 29%). Five (1.5%) patients treated with REMICADE and MTX experienced more prolonged elevations in their ALT.

OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis

The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed with additional 3 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Remicade should be given in combination with methotrexate.

Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as a single intravenous infusion for treatment of moderately to severely active Crohn's disease. In patients with fistulizing disease, an initial 5 mg/kg dose should be followed with additional 5 mg/kg doses at 2 and 6 weeks after the first infusion.

There are insufficient safety and efficacy data for the use of REMICADE in Crohn's disease beyond the recommended duration (see *WARNINGS, Hypersensitivity; ADVERSE REACTIONS, Infusion-related Reactions;* and *INDICATIONS AND USAGE*).

Preparation and administration instructions: Use aseptic technique.

REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE solution required.
2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow

Continued on next page

Remicade—Cont.

and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.
4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2-µm or less). Any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

HOW SUPPLIED

REMICADE (infliximab) lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength:

NDC 57894-030-01 100 mg infliximab in a 20-mL vial

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1-800-457-6399 9 November 1999

Shown in Product Identification Guide, page 310

RETAVASE®

Reteplase, recombinant

℞

DESCRIPTION

Retavase® (Reteplase) is a non-glycosylated deletion mutein of tissue plasminogen activator (tPA), containing the kringle 2 and the protease domains of human tPA. Retavase® contains 355 of the 527 amino acids of native tPA (amino acids 1–3 and 176–527). Retavase® is produced by recombinant DNA technology in E. coli. The protein is isolated as inactive inclusion bodies from E. coli, converted into its active form by an in vitro folding process and purified by chromatographic separation. The molecular weight of Reteplase is 39,571 daltons.

Potency is expressed in units (U) using a reference standard which is specific for Retavase® and is not comparable with units used for other thrombolytic agents.

Retavase® is a sterile, white, lyophilized powder for intravenous bolus injection after reconstitution with Sterile Water for Injection, USP (without preservatives). Following reconstitution, the pH is 6.0 ± 0.3. Retavase® is supplied as a 10.4 U vial to ensure sufficient drug for administration of each 10 U dose. Each single-use vial contains:

10.4 U (18.1 mg) Vial	
Reteplase	18.1 mg
Tranexamic Acid	8.32 mg
Dipotassium Hydrogen Phosphate	136.24 mg
Phosphoric Acid	51.27 mg
Sucrose	364.0 mg
Polysorbate 80	5.20 mg

CLINICAL PHARMACOLOGY

General

Retavase® is a recombinant plasminogen activator which catalyzes the cleavage of endogenous plasminogen to generate plasmin. Plasmin in turn degrades the fibrin matrix of the thrombus, thereby exerting its thrombolytic action.[1,2] In a controlled trial, 36 of 56 patients treated for an acute myocardial infarction (AMI) had a decrease in fibrinogen levels to below 100 mg/dL by 2 hours following the administration of Retavase® as a double-bolus intravenous injection (10 + 10 U) in which 10 U (17.4 mg) was followed 30 minutes later by a second bolus of 10 U (17.4 mg).[3] The mean fibrinogen level returned to the baseline value by 48 hours.

Pharmacokinetics

Based on the measurement of thrombolytic activity, Retavase® is cleared from plasma at a rate of 250–450 mL/min, with an effective half-life of 13–16 minutes. Retavase® is cleared primarily by the liver and kidney.

Clinical Studies

The safety and efficacy of Retavase® were evaluated in three controlled clinical trials in which Retavase® was compared to other thrombolytic agents. The INJECT study was designed to assess the relative effects of Retavase® or the Streptase® brand of Streptokinase upon mortality rates at 35 days following an AMI. The other studies (RAPID 1 and RAPID 2) were arteriographic studies which compared the effect on coronary patency of Retavase® to two regimens of Alteplase (a tissue plasminogen activator; Activase® in the USA and Actilyse® in Europe) in patients with an AMI. In all three studies, patients were treated with aspirin (initial doses of 160 mg to 350 mg and subsequent doses of 75 mg to 350 mg) and heparin (a 5,000 U IV bolus prior to the administration of Retavase®, followed by a 1000 U/hour continuous IV infusion for at least 24 hours).[3,4,5] The safety and efficacy of Retavase® have not been evaluated using antithrombotic or antiplatelet regimens other than those described above.

Retavase® (10 + 10 U) was compared to Streptokinase (1.5 million units over 60 minutes) in a double-blind, randomized, European study (INJECT), which studied 6,010 patients treated within 12 hours of the onset of symptoms of AMI. To be eligible for enrollment, patients had to have chest pain consistent with coronary ischemia and ST segment elevation, or a bundle branch block pattern on the EKG. Patients with known cerebrovascular or other bleeding risks or those with a systolic blood pressure >200 mm Hg or a diastolic blood pressure >100 mm Hg were excluded from enrollment. The results of the primary endpoint (mortality at 35 days), six month mortality and selected other 35 day endpoints are shown in Table 1 for patients receiving study medications.

[See table 1 below]

Table 1
INJECT TRIAL
Incidence of Selected Outcomes

Enpoint	Retavase® n = 2,965	Streptokinase n = 2,971	Retavase®-Streptokinase difference (95% CI)
35 Day mortality	8.9%	9.4%	-0.5 (-2.0, 0.9)
6 Month mortality†	11.0%	12.1%	-1.1 (-2.7, 0.6)
Combined outcome of 35 day mortality or nonfatal stroke within 35 days	9.6%	10.2%	-0.6 (-2.1, 1.0)
Heart failure	24.8%	28.1%	-3.3 (-5.6, -1.1)
Cardiogenic shock	4.6%	5.8%	-1.2 (-2.4, -0.1)
Any stroke	1.4%	1.1%	0.3 (-0.3, 0.8)
Intrancranial hemorrhage	0.8%	0.4%	0.4 (0.0, 0.8)

*p value for the exploratory analysis comparing Retavase® versus Streptokinase.
†Kaplan-Meier estimates.

For morality, stroke and the combined outcome of ... or stroke, the 95% confidence intervals in Table 1 ... range within which the true difference in outcome ... lies and includes the possibility of no difference. ... dences of congestive heart failure and of cardio... were significantly lower among patients tre... Retavase®.

The total incidence of stroke was similar be... groups. However, more patients treated with Re... perienced hemorrhagic strokes than patients tre... Streptokinase. An exploratory analysis indicated ... incidence of intracranial hemorrhage was high... older patients or those with elevated blood pressu... cidence of intracranial hemorrhage among the ... treated with Retavase® who were older than 70 ... 2.2%. Intracranial hemorrhage occurred in ... (2.4%) patients treated with Retavase® who had ... systolic blood pressure >160 mm Hg and in 15 of ... (0.6%) Retavase® patients who had an initial sy... pressure <160 mm Hg.

Two arteriographic studies (RAPID 1 and RAPID ... performed utilizing open-label administration of ... agents and a blinded review of the arteriograms. In ... 1, patients were treated within 6 hours of the onset ... toms, and in RAPID 2, patients were treated ... 12 hours of the onset of symptoms. Both studies ... coronary artery perfusion through the infarct-rela... 90 minutes after the initiation of therapy as the ... endpoint. Some patients in each study also had ... through the infarct-related artery evaluated at 60 ... after the initiation of therapy. In RAPID 1, Reta... doses of 10 + 10 U, 15 U, or 10 + 5 U) was com... 3 hour regimen of Alteplase (100 mg adminis... hrs). In RAPID 2, Retavase® (10 + 10 U) was co... an accelerated regimen of Alteplase (100 mg ad... over 1.5 hrs). The percentages of patients with ... complete flow (TIMI grades 2 or 3) and complete ... grade 3), are shown along with ventricular functio... ments in Table 2. The follow-up arteriogram was ... at a median of 8 (RAPID 1) and 5 (RAPID 2) days ... the administration of the thrombolytics. In RAP... best patency results were obtained with the 10+... In RAPID 2, the percentage of patients with part... plete flow and the percentage of patients with co... was significantly higher with Retavase® than ... teplase at 90 minutes after the initiation of the... clinical trials the reocclusion rates were ... Retavase® and Alteplase. The relationship be... nary artery patency and clinical efficacy has not b... lished.

[See table 2 at bottom of next page]

Approximately 70% (RAPID 1) and 78% (RAPID ... patients in the arteriographic studies under... arteriography at 60 minutes following the admi... the study agents. In both trials the percentage ... with complete flow at 60 minutes was signific... with Retavase® than with Alteplase. Neither ... cal trial was designed nor powered to compare ... or safety of Retavase® and Alteplase with respe... comes of mortality and stroke.

INDICATIONS AND USAGE

Retavase® (Reteplase) is indicated for use in t... ment of acute myocardial infarction (AMI) in ad... improvement of ventricular function following AM... duction of the incidence of congestive heart failu... reduction of mortality associated with AMI. ... should be initiated as soon as possible after the o... symptoms (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk ... ing, Retavase® is contraindicated in the follow... tions:

- **Active internal bleeding**
- **History of cerebrovascular accident**
- **Recent intracranial or intraspinal surgery or ... WARNINGS)**

Table 1
Adverse Events ≥5% of Patients (N=315)

	Incidence All Grades	
	N	%
...rse Event	275	87
...A Whole		
...	154	49
...	102	32
...	49	16
...he	43	14
... Irritation	19	6
...inal Pain	18	6
...ascular System		
...nsion	32	10
...e System		
...	55	18
...	23	7
...ing		
... and Lymphatic System		
...penia	33	11
...ocytopenia	25	8
...penia	21	7
...c and Nutritional System		
...dema	41	13
...-Skeletal System		
...	21	7
... System	23	7
...ess		
...tory System		
...	25	8
...hospasm	24	8
... Appendages		
...	32	10
...	31	10
...	24	8

...pulmonary symptoms and culminated in death sev... ...this following the last RITUXAN infusion. The ... resumption or continued administration of ...AN in patients with pneumonitis or bronchiolitis ob... ...is unknown.

... above]

...and life-threatening (Grade 3 and 4) events were re... ...in 10% (32/315) of patients. The following Grade 3 ...adverse events were reported: neutropenia (1.9%), ...(1.5%), leukopenia and thrombocytopenia (1.3% for ...hypotension, anemia, bronchospasm, and urticaria ...each), headache, abdominal pain, and arrhythmia ...each), asthenia, hypertension, nausea, vomiting, ...disorder, angioedema, arthralgia, pain, rhinitis, ...cough, dyspnea, bronchiolitis obliterans, hypoxia, ...pruritus, and rash (one patient each, 0.3%).

...ing adverse events occurred in ≥1.0% but <5.0% ..., in order of decreasing incidence: flushing, ar... ...diarrhea, anemia, cough increase, hypertension, ...disorder, pain, hyperglycemia, back pain, pe... ...edema, paresthesia, dyspepsia, chest pain, ano... ...ety, malaise, tachycardia, agitation, insomnia, si... ...conjunctivitis, abdominal enlargement, postural hy... ...LDH increase, hypocalcemia, hypesthesia, ...disorder, tumor pain, pain at injection site, ...ia, hypertonia, nervousness, bronchitis, and taste ...

...adverse events—The following serious adverse ...have been reported at a frequency of less than ...postmarketing setting:

...Whole: Lupus-like syndrome and serum sickness

...ular System: Systemic vasculitis

...etal System: Polyarticular arthritis

... System: Pleuritis

...Appendages: Severe bullous skin reactions (in... ...epidermal necrolysis) and pemphigus; some ...come

...: Optic neuritis and uveitis

...se events were reported as individual compo... ...system processes (e.g., optic neuritis in a pa... ...ystemic vasculitis, pleuritis in association with ...ndrome, etc.) and often in conjunction with ...arthritis.

...of patients reporting any adverse event was ...ents with bulky disease and those with le... ...in diameter. However, the incidence of dizzi... ...enia, thrombocytopenia, myalgia, anemia, and ...higher in patients with lesions >10 cm. The ...y Grade 3 and 4 event was higher (31% vs. ...ncidence of Grade 3 or 4 neutropenia, anemia, ...nd dyspnea was also higher in patients with ...compared with patients with lesions <10 cm.

...GE

...no experience with overdosage in human ...ingle doses higher than 500 mg/m^2 have not ...

...D ADMINISTRATION

...ed dosage of RITUXAN is 375 mg/m^2 given ...once weekly for four doses (Days 1, 8, 15, ...UXAN may be administered in an outpatient ...NOT ADMINISTER AS AN INTRAVENOUS ...US. (See Administration).

... Administration

... Administration: Use appropriate aseptic ...draw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion are stable at 2–8°C (36–46°F) for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see WARNINGS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion-related events. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: Subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated.

Stability and Storage: RITXUAN vials are stable at 2–8°C (36–46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight.

HOW SUPPLIED

RITUXAN is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).

NDC 50242-051-21

Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).

NDC 50242-053-06

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ENBREL®
[ĕn-brĕl]
(etanercept)

DESCRIPTION

ENBREL (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

ENBREL is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration after reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol). Following reconstitution, the solution of ENBREL is clear and colorless, with a pH of 7.4 ± 0.3. Each single-use vial of ENBREL contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

CLINICAL PHARMACOLOGY

General

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and the resulting joint pathology.[1, 2] Elevated levels of TNF are found in the synovial fluid of RA patients.[3] Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist natu-

Continued on next page

Enbrel—Cont.

rally as monomeric molecules on cell surfaces and in soluble forms.[4] Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF in vitro and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.[5, 6] Etanercept inhibits binding of both TNFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface TNFRs, rendering TNF biologically inactive.[6] Cells expressing transmembrane TNF that bind ENBREL are not lysed in vitro in the presence or absence of complement.[6]

Etanercept can also modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (i.e., E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).[6]

Pharmacokinetics

After administration of 25 mg of ENBREL by a single subcutaneous (SC) injection to three patients with RA, a median half-life of 115 hours (range 98 to 300 hours) was observed with a clearance of 89 mL/hr (52 mL/hr/m^2). A maximum serum concentration (Cmax) of 1.2 mcg/mL (range 0.6 to 1.5 mcg/mL) and time to Cmax of 72 hours (range 48 to 96 hours) was observed in these patients. After continued dosing of RA patients (N=25) with ENBREL for 6 months with 25 mg twice weekly, the median observed level was 3.0 mcg/mL (range 1.7 to 5.6 mcg/mL). Based on the available data, individual patients may undergo a two- to five-fold increase in serum levels with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months.

Pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment or interactions with methotrexate.

Pediatric patients with JRA (ages 4 to 17 years) were administered 0.4 mg/kg of ENBREL for up to 18 weeks. The average serum concentration after repeated dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Preliminary data suggests that the clearance of ENBREL is reduced slightly in children ages 4 to 8 years. Children < 4 years of age have not been studied.

CLINICAL STUDIES

Adult Rheumatoid Arthritis

The safety and efficacy of ENBREL were assessed in three randomized, double-blind, controlled studies. Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs; e.g., hydroxychloroquine, oral or injectable gold, methotrexate [MTX], azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hour, CRP > 20 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL or placebo were administered SC twice a week for 6 consecutive months. Results from patients receiving 25 mg are presented below.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that subjects in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/wk) for at least 4 weeks and they had at least 6 tender or painful joints. Subjects in Study II received a dose of 25 mg ENBREL or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of ENBREL to MTX in patients with active RA. This study evaluated 632 patients who were ≥18 years old with early (≤ 3 years disease duration) active RA; had never received treatment with MTX; and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL were administered SC twice a week for 12 consecutive months. Results from patients receiving 25 mg are presented below. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or ENBREL doses, respectively.

The results of all three trials were expressed in percentage of patients with improvement in RA using American College of Rheumatology (ACR) response criteria.[7]

Clinical Response

The percent of ENBREL-treated patients achieving ACR 20, 50, and 70 responses was consistent across all three trials. The results of the three trials are summarized in Table 1.

[See table 1 above]

The time course for ACR 20 response rates for patients receiving placebo or 25 mg ENBREL in Studies I and II is summarized in Figure 1. The time course of responses to ENBREL in Study III was similar.

[See figure 1 in next column]

Among patients receiving ENBREL, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III: 25 mg ENBREL was more effective than 10 mg (10 mg was not evaluated in Study II). ENBREL was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, approximately 10% of patients treated with ENBREL achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. The results of the components of the ACR response criteria for Study I are shown in Table 2. Findings were similar in Studies II and III for patients treated with ENBREL.

[See table 2 above]

After discontinuation of ENBREL, symptoms of arthritis generally returned within a month. Reintroduction of treatment with ENBREL after discontinuations of up to 18 months resulted in the same magnitudes of response as patients who received ENBREL without interruption. Continued therapy based on results of open-label studies. Continued responses have been seen for up to 36 months in open-label extension treatment trials when patients received ENBREL without interruption.

A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during Studies I and II. Subdomains of the HAQ were improved in patients treated with ENBREL.

In Study III, health outcome measures were assessed using the SF-36 questionnaire. The eight subscales of the SF-36 were combined into two summary scales, the physical component summary (PCS) and the mental component summary (MCS).[9] At 12 months, patients treated with ENBREL showed significantly more improvement as compared to the 10 mg ENBREL group, but not in

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in total Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were read at baseline, 6 months, and 12 months. The results are shown in Table 3. A significant difference in change in erosion score was observed at 6 months and maintained at 12 months.

[See table 3 above]

Polyarticular-Course Juvenile Rheumatoid Arthritis

The safety and efficacy of ENBREL were assessed in a part study in 69 children with polyarticular-course JRA who had a variety of JRA onset types. Patients ages 4 to 17 with moderately to severely active polyarticular JRA refractory to or intolerant of methotrexate were patients remained on a stable dose of a single non-anti-inflammatory drug and/or prednisone (≤ 0.2 or 10 mg maximum). In part 1, all patients

Table 1: ACR Responses in Placebo- and Active-Controlled Trials (Percent of Patients)

	Placebo Controlled				Active Control
	Study I		Study II		Study III
Response	Placebo N = 80	ENBREL[a] N = 78	MTX/ Placebo N = 30	MTX/ ENBREL[a] N = 59	MTX N = 217
ACR 20					
Month 3	23%	62%[b]	33%	66%[b]	56%
Month 6	11%	59%[b]	27%	71%[b]	58%
Month 12	NA	NA	NA	NA	65%
ACR 50					
Month 3	8%	41%[b]	0%	42%[b]	24%
Month 6	5%	40%[b]	3%	39%[b]	32%
Month 12	NA	NA	NA	NA	43%
ACR 70					
Month 3	4%	15%[b]	0	15%[b]	7%
Month 6	1%	15%[b]	0	15%[b]	14%
Month 12	NA	NA	NA	NA	22%

a. 25 mg ENBREL SC twice weekly.
b. $p < 0.01$, ENBREL vs. placebo.
c. $p < 0.05$, ENBREL vs. MTX.

Table 2: Components of ACR Response in Study I

	Placebo N = 80		ENBREL[a] N = 78	
Parameter (median)	Baseline	3 Months	Baseline	3
Number of tender joints[b]	34.0	29.5	31.2	10.0
Number of swollen joints[c]	24.0	22.0	23.5	8.0
Physician global assessment[d]	7.0	6.5	7.0	1.0
Patient global assessment[d]	7.0	7.0	7.0	1.0
Pain[d]	6.9	6.6	6.9	1.4
Disability index[e]	1.7	1.8	1.6	1.0
ESR (mm/hour)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

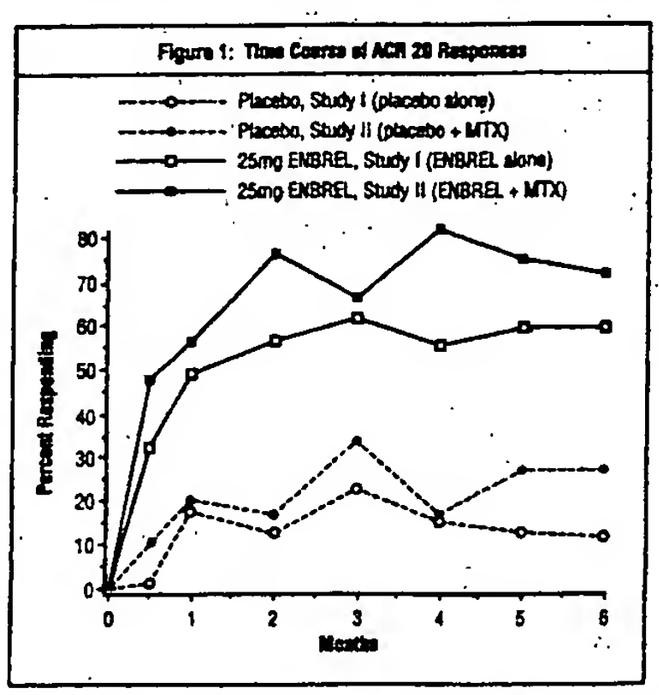
** Results at 6 months showed similar improvement.*
a. 25 mg ENBREL SC twice weekly.
b. Scale 0–71.
c. Scale 0–68.
d. Visual analog scale; 0 = best, 10 = worst.
e. Health Assessment Questionnaire[8]; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, walking, hygiene, reach, grip, and activities.
f. $p < 0.01$, ENBREL vs. placebo, based on mean percent change from baseline.

Table 3: Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg ENBREL	MTX-ENBREL (95% Confidence Interval*)
12 Months	Total Sharp score	1.59	1.00	0.59 (−0.12, 1.30)
	Erosion score	1.03	0.47	0.56 (0.11, 1.00)
	JSN score	0.56	0.52	0.04 (−0.39, 0.46)
6 Months	Total Sharp score	1.06	0.57	0.49 (0.06, 0.91)
	Erosion score	0.68	0.30	0.38 (0.09, 0.66)
	JSN score	0.38	0.27	0.11 (−0.14, 0.35)

** 95% confidence intervals for the differences in change scores between MTX and ENBREL*

Figure 1: Time Course of ACR 20 Responses



(maximum 25 mg per dose) ENBREL SC twice ly. In part 2, patients with a clinical response at day 90 randomized to remain on ENBREL or receive placebo ur months and assessed for disease flare. Responses measured using the JRA Definition of Improvement defined as ≥ 30% improvement in at least three of ≥ 30% worsening in no more than one of six JRA set criteria, including active joint count, limitation of physician and patient/parent global assessments, onal assessment, and ESR. Disease flare was defined ≥ 30% worsening in three of the six JRA core set cri- and ≥ 30% improvement in not more than one of the RA core set criteria and a minimum of two active joints. art 1 of the study, 51 of 69 (74%) patients demonstrated nical response and entered part 2.[11] In part 2, 6 of 25 patients remaining on ENBREL experienced a dis- flare compared to 20 of 26 (77%) patients receiving pla- ($p = 0.007$). From the start of part 2, the median time to was ≥ 116 days for patients who received ENBREL 28 days for patients who received placebo. Each compo- of the JRA core set criteria worsened in the arm that ved placebo and remained stable or improved in the that continued on ENBREL. The data suggested the ibility of a higher flare rate among those patients with a baseline ESR. Of patients who demonstrated a clin- response at 90 days and entered part 2 of the study, of the patients remaining on ENBREL continued to rove from month 3 through month 7, while those who ved placebo did not improve.

The majority of JRA patients who developed a disease flare part 2 and reintroduced ENBREL treatment up to 4 nths after discontinuation re-responded to ENBREL rapy, in open-label studies. Most of the responding pa- who continued ENBREL therapy without interrup- have maintained responses for up to 18 months.

ies have not been done in patients with polyarticular- JRA to assess the effects of continued ENBREL ther- in patients who do not respond within 3 months of ini- ENBREL therapy, or to assess the combination of EL with methotrexate.

nogenicity

ients were tested at multiple timepoints for antibodies to BREL. Antibodies to ENBREL, all non-neutralizing, detected at least once in sera of < 16% of adult rheu- arthritis patients. No apparent correlation of anti- development to clinical response or adverse events was ed. Results from JRA patients were similar to those in adult RA patients treated with ENBREL. The long- immunogenicity of ENBREL is unknown.

data reflect the percentage of patients whose test re- were considered positive for antibodies to ENBREL in LISA assay, and are highly dependent on the sensitiv- specificity of the assay. Additionally, the observed ce of antibody positivity in an assay may be influ- by several factors including sample handling, concom- medications, and underlying disease. For these rea- comparison of the incidence of antibodies to ENBREL the incidence of antibodies to other products may be ing.

CATIONS AND USAGE

is indicated for reducing signs and symptoms and structural damage in patients with moderately to active rheumatoid arthritis. ENBREL can be used nation with methotrexate in patients who do not adequately to methotrexate alone.

is indicated for reducing signs and symptoms of ely to severely active polyarticular-course juvenile arthritis in patients who have had an inade- sponse to one or more DMARDs.

INDICATIONS

should not be administered to patients with sepsis known hypersensitivitiy to ENBREL or any of its

GS

MARKETING REPORTS, SERIOUS INFECTIONS IS, INCLUDING FATALITIES, HAVE BEEN RE- ITH THE USE OF ENBREL. MANY OF THESE SE- NTS HAVE OCCURRED IN PATIENTS WITH UN- DISEASES THAT IN ADDITION TO THEIR RHEU- ARTHRITIS COULD PREDISPOSE THEM TO S. PATIENTS WHO DEVELOP A NEW INFECTION NDERGOING TREATMENT WITH ENBREL E MONITORED CLOSELY. ADMINISTRATION OF OULD BE DISCONTINUED IF A PATIENT DEVEL- RIOUS INFECTION OR SEPSIS. TREATMENT REL SHOULD NOT BE INITIATED IN PATIENTS IVE INFECTIONS INCLUDING CHRONIC OR LO- NFECTIONS. PHYSICIANS SHOULD EXERCISE WHEN CONSIDERING THE USE OF ENBREL IN WITH A HISTORY OF RECURRING INFECTIONS UNDERLYING CONDITIONS WHICH MAY PREDIS- NTS TO INFECTIONS, SUCH AS ADVANCED OR CONTROLLED DIABETES (see PRECAUTIONS, REACTIONS, Infections).

TIONS

actions associated with administration of EN- ng clinical trials have been reported in < 2% of an anaphylactic reaction or other serious aller- occurs, administration of ENBREL should be d immediately and appropriate therapy initi-

Table 4: Percent of RA Patients Reporting Adverse Events In Controlled Clinical Trials*

Event	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
	Placebo† (n = 152)	ENBREL (n = 349)	MTX (n = 217)	ENBREL (n = 415)
Injection site reaction	10	37	7	34
Infection	32	35	72	64
Non-upper respiratory infection**	32	38	60	51
Upper respiratory infection**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	–	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis ("MTX lung")	–	–	2	0

** Includes data from the 6-month study in which patients received concurrent MTX therapy.*
† The duration of exposure for patients receiving placebo was less than the ENBREL-treated patients.
*** Includes data from two placebo-controlled trials.*

Information to Patients
If a patient or caregiver is to self-administer ENBREL, he/she should be instructed in injection techniques and how to measure the correct dose to help ensure the proper administration of ENBREL (see **How to Use ENBREL, Instructions for Preparing and Giving an Injection**). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to self-inject subcutaneously should be assessed. A puncture-resistant container for disposal of needles and syringes should be used. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Immunosuppression
The possibility exists for anti-TNF therapies, including ENBREL, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL on the development and course of malignancies as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections** and **Malignancies**). The safety and efficacy of ENBREL in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations
No data are available on the effects of vaccination in patients receiving ENBREL. Live vaccines should not be given concurrently with ENBREL. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL (see **PRECAUTIONS, Immunosuppression**).
It is recommended that JRA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL therapy. Two JRA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoantibody Formation
Treatment with ENBREL may result in the formation of autoimmune antibodies (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions
Specific drug interaction studies have not been conducted with ENBREL.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

Pregnancy (Category B)
Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to ENBREL. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether ENBREL is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ENBREL, a decision should be made whether to discontinue nursing or to discontinue the drug.

Geriatric Use
A total of 197 RA patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use
ENBREL is indicated for treatment of polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. For issues relevant to pediatric patients, in addition to other sections of the label, see also **PRECAUTIONS, Immunizations**, and **ADVERSE REACTIONS, Adverse Reactions in Pediatric Patients**. ENBREL has not been studied in children < 4 years of age.

ADVERSE REACTIONS

ENBREL has been studied in 1197 patients with RA, followed for up to 36 months. The proportion of patients who discontinued treatment due to adverse events was approximately 4% in both ENBREL and placebo-treated patients.

Injection Site Reactions
In controlled trials, 37% of patients treated with ENBREL developed injection site reactions. All injection site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given.

Infections
In controlled trials, there were no differences in rates of infection among patients treated with ENBREL and those treated with placebo or MTX. The most common type of infection was upper respiratory infection, which occurred in 16% of placebo-treated patients and 29% of patients treated with ENBREL. When the longer observation of patients on ENBREL was accounted for, the event rate was similar in both groups.
In placebo-controlled trials in DMARD-refractory RA, no increase in the incidence of serious infections was observed (approximately 1% in both placebo and ENBREL-treated groups). The rates of infections for the ENBREL arm in Study III were similar. In all clinical trials in RA, 50 of 1197 subjects exposed to ENBREL for up to 36 months experienced serious infections, including pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL. Some have occurred within a few weeks after initiating treatment with ENBREL. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. (See **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL treatment may increase mortality in patients with established sepsis.[12]

Continued on next page

Enbrel—Cont.

Malignancies
Seventeen malignancies of various types were observed in 1197 RA patients treated in clinical trials with ENBREL for up to 36 months. The observed rates and incidences were similar to those expected for the population studied.
Autoantibodies
Patients had serum samples tested for autoantibodies at multiple timepoints. In Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with ENBREL (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with ENBREL compared to 4% of placebo-treated patients) and by crithidia lucilae assay (3% of patients treated with ENBREL compared to none of placebo-treated patients). The proportion of patients treated with ENBREL who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In Study III, no pattern of increased autoantibody development was seen in ENBREL patients compared to MTX patients. No patients in placebo- and active-controlled trials developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with ENBREL on the development of autoimmune diseases is unknown.
Other Adverse Reactions
Table 4 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III.
[See table 4 at top of previous page]
Among patients with rheumatoid arthritis treated in placebo-controlled trials, serious adverse events occurred at a frequency of 4% in 349 patients treated with ENBREL compared to 5% of 152 placebo-treated patients. In Study III, serious adverse events occurred at a frequency of 6% in 415 patients treated with ENBREL compared to 8% of 217 MTX-treated patients. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL, malignancies (see **ADVERSE REACTIONS, Malignancies**) and infections (see **ADVERSE REACTIONS, Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed included heart failure, myocardial infarction, myocardial ischemia, cerebral ischemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal hemorrhage, bursitis, depression, dyspnea, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, and thrombophlebitis.
Adverse Reactions in Pediatric Patients
In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients. Differences from adult and other special considerations are discussed in the following paragraphs.
Severe adverse reactions reported in 69 JRA patients ages 4 to 17 years included varicella (see also **PRECAUTIONS, Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.
Forty-three of 69 (62%) children with JRA experienced an infection while receiving ENBREL during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JRA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations.
The following adverse events were reported more commonly in 69 JRA patients receiving 3 months of ENBREL compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 events per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

OVERDOSAGE

The maximum tolerated dose of ENBREL has not been established in humans. Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of ENBREL. Single IV doses up to 60 mg/m^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities. The highest dose level evaluated in RA patients has been a single IV loading dose of 32 mg/m^2 followed by SC doses of 16 mg/m^2 (~25 mg) administered twice weekly. In one RA trial, one patient mistakenly self-administered 62 mg ENBREL SC twice weekly for 3 weeks without experiencing adverse effects.

DOSAGE AND ADMINISTRATION

The recommended dose of ENBREL for adult patients with rheumatoid arthritis is 25 mg given twice weekly as a subcutaneous injection 72–96 hours apart (see **Clinical Studies**). Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics may be continued during treatment with ENBREL. Higher doses of ENBREL have not been studied.
The recommended dose of ENBREL for pediatric patients ages 4 to 17 years with active polyarticular-course JRA is 0.4 mg/kg (up to a maximum 25 mg per dose) given twice weekly as a subcutaneous injection 72–96 hours apart. Glucocorticoids, nonsteroidal anti-inflamatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL. Concurrent use with methotrexate and higher doses of ENBREL have not been studied in pediatric patients.
Preparation of ENBREL
ENBREL is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in how to measure the correct dose and in injection technique.
Note: The needle cover of the diluent syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.
ENBREL should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of ENBREL. During reconstitution of ENBREL, the diluent should be injected very slowly into the vial. Some foaming will occur. This is normal. To avoid excessive foaming, **do not shake or vigorously agitate**. The contents should be swirled gently during dissolution. Generally, dissolution of ENBREL takes less than 10 minutes. The reconstituted solution should be clear and colorless and used within 6 hours (see **Storage and Stability**).
Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains. Withdraw the solution into a syringe, removing only the dose to be given from the vial. Some foam or bubbles may remain in the vial.
No other medications should be added to solutions containing ENBREL, and do not reconstitute ENBREL with other diluents. Do not filter reconstituted solution during preparation or administration.
Rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red, or hard. (See **How to Use ENBREL, Instructions for Preparing and Giving an Injection** instruction sheet.)
Storage and Stability
Do not use a dose tray beyond the date stamped on the carton, dose tray label, vial label, or diluent syringe label. The dose tray containing ENBREL (sterile powder) must be refrigerated at 2–8°C (36–46°F). DO NOT FREEZE.
Administer reconstituted solutions of ENBREL as soon as possible after reconstitution. If not administered immediately after reconstitution, ENBREL may be stored in the vial at 2–8° (36–46°F) for up to 6 hours. **ANY ENBREL NOT USED WITHIN 6 HOURS OF RECONSTITUTION SHOULD BE DISCARDED. PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED.**

HOW SUPPLIED

ENBREL is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg single-use vial of etanercept, one syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one plunger, and two alcohol swabs.
Rx only

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Marketed by Immunex Corporation and W
Pharmaceuticals

LEUKINE®
SARGRAMOSTIM

Caution: Federal law prohibits dispensing wit
scription.

DESCRIPTION

LEUKINE® (sargramostim) is a recombinant hu
ulocyte-macrophage colony stimulating factor (
CSF) produced by recombinant DNA technology i
(S. cerevisiae) expression system. GM-CSF is a hu
etic growth factor which stimulates proliferation a
entiation of hematopoietic progenitor cells. LEUK
glycoprotein of 127 amino acids characterized by t
molecular species having molecular masses of
16,800 and 15,500 daltons. The amino acid seq
LEUKINE differs from the natural human GM-C
substitution of leucine at position 23, and the carb
moiety may be different from the native protein.
mostim has been selected as the proper name f
derived rhu GM-CSF.
The LEUKINE Liquid presentation is formulated
ile, preserved (1.1% benzyl alcohol), injectable solu
mcg/mL) in a vial. Lyophilized LEUKINE is a steri
preservative-free powder (250 mcg) that requires r
tution with 1 mL Sterile Water for Injection, USP
Bacteriostatic Water for Injection, USP.
LEUKINE Liquid and reconstituted lyophilized L
are clear, colorless liquids suitable for subcutane
tion or intravenous infusion. LEUKINE Liquid con
mcg (2.8×10^6 IU/mL) sargramostim and 1.1% ben
hol in a 1 mL solution. The vial of lyophilized LE
contains 250 mcg (1.4×10^6 IU/vial) sargramos
LEUKINE Liquid vial and reconstituted lyophilized
INE vial also contain 40 mg/mL mannitol, USP; 1
sucrose, NF; and 1.2 mg/mL tromethamine, USP
ents. Biological potency is expressed in Internationa
(IU) as tested against the WHO First International
ence Standard. The specific activity of LEUKINE
imately 5.6×10^6 IU/mg.

CLINICAL PHARMACOLOGY

General GM-CSF belongs to a group of growth
termed colony stimulating factors which support
clonal expansion, and differentiation of hematopo
genitor cells. GM-CSF induces partially committed
itor cells to divide and differentiate in the gra
macrophage pathways.
GM-CSF is also capable of activating mature gr
and macrophages. GM-CSF is a multilineage fact
addition to dose-dependent effects on the myelo
lineage, can promote the proliferation of megak
and erythroid progenitors.[1] However, other facto
quired to induce complete maturation in these two
The various cellular responses (i.e., division, m
activation) are induced through GM-CSF binding
receptors expressed on the cell surface of target ce
***In vitro* Studies of LEUKINE in Human Cells** The b
activity of GM-CSF is species-specific. Consequently
tro studies have been performed on human cells to
terize the pharmacological activity of LEUKINE.
exposure of human bone marrow cells to LEUKIN
centrations ranging from 1–100 ng/mL results in th
eration of hematopoietic progenitors and in the for
pure granulocyte, pure macrophage and mixed gran
macrophage colonies.[3] Chemotactic, anti-fungal a
parasitic[4] activities of granulocytes and monocytes
creased by exposure to LEUKINE *in vitro*. LEUK
creases the cytotoxicity of monocytes toward
neoplastic cell lines[3] and activates polymorphonuc
trophils to inhibit the growth of tumor cells.
***In vivo* Primate Studies of LEUKINE** Pharmacolog
ogy studies of LEUKINE were performed in cyn
monkeys. An acute toxicity study revealed an ab
treatment-related toxicity following a single IV bol
tion at a dose of 300 mcg/kg. Two subacute studies
formed using IV injection (maximum dose 200 mcg/k
14 days) and subcutaneous injection (maximum d
mcg/kg/day × 28 days). No major visceral organ toxi
documented. Notable histopathology findings inclu
creased cellularity in hematologic organs and h
lung tissues. A dose-dependent increase in leukocyt
which consisted primarily of segmented neutrop
curred during the dosing period; increases in monocy
sophils, eosinophils and lymphocytes were also not
kocyte counts decreased to pretreatment values ov
week recovery period.
Pharmacokinetics Pharmacokinetic profiles have b
alyzed in controlled studies of 24 normal male volu

Effexor-XR—Cont.

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Effexor XR (venlafaxine hydrochloride) extended-release capsules is not a controlled substance.

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Discontinuation effects have been reported in patients receiving venlafaxine (see **"DOSAGE AND ADMINISTRATION"**).

While venlafaxine has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Among the patients included in the premarketing evaluation of Effexor XR, there were 2 reports of acute overdosage with Effexor XR in depression trials, either alone or in combination with other drugs. One patient took a combination of 6 g of Effexor XR and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.85 g of Effexor XR. This patient reported paresthesia of all four limbs but recovered without sequelae.

There were 2 reports of acute overdose with Effexor XR in GAD trials. One patient took a combination of 0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem. This patient was described as being alert, able to communicate, and a little sleepy. This patient was hospitalized, treated with activated charcoal, and recovered without any untoward effects. The other patient took 1.2 g of Effexor XR. This patient recovered and no other specific problems were found. The patient had moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. These symptoms resolved over the next week.

Among the patients included in the premarketing evaluation with Effexor, there were 14 reports of acute overdose with venlafaxine, either alone or in combination with other drugs and/or alcohol. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g, and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported.

Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of venlafaxine, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water.

Initial Treatment

Depression

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of Effexor XR in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for Effexor XR has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140–180 mg/day (see **"Clinical Trials"** under **"CLINICAL PHARMACOLOGY"**).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for Effexor (the immediate release form of venlafaxine), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225 mg/day is very limited.

Generalized Anxiety Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Generalized Anxiety Disorder (GAD), the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in GAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days.

Switching Patients from Effexor Tablets

Depressed patients who are currently being treated at a therapeutic dose with Effexor may be switched to Effexor XR at the nearest equivalent dose (mg/day), e.g., 37.5 mg venlafaxine two-times-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

Patients with Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see **"CLINICAL PHARMACOLOGY"**), it is recommended that the starting dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, individualization of dosage may be desirable in some patients.

Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10–70 mL/min) compared with normal subjects (see **"CLINICAL PHARMACOLOGY"**), it is recommended that the total daily dose be reduced by 25%–50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50% and that the dose be withheld until the dialysis treatment is completed (4 hrs). Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients

No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of depression or generalized anxiety disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long patients with depression or generalized anxiety disorder should be treated with Effexor XR.

It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown

In patients with Generalized Anxiety Disorder, there are no efficacy data beyond eight weeks of treatment with Effexor XR. The need for continuing medication in patients with GAD who improve with Effexor XR treatment should be periodically reassessed.

Discontinuing Effexor XR

When discontinuing Effexor XR after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Patients who have received Effexor XR for 6 weeks or more should have their dose tapered over at least a 2-week period. In clinical trials with Effexor XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary. Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in depression. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting. It is therefore recommended that the dosage of Effexor XR be tapered gradually and the patient monitored. The period required for tapering may depend on the dose, duration of therapy and the individual patient. Discontinuation effects are well known to occur with antidepressants.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **"CONTRAINDICATIONS"** and **"WARNINGS"**).

HOW SUPPLIED

Effexor® XR (venlafaxine hydrochloride) extended-release capsules are available as follows:

37.5 mg, grey cap/peach body with "w" and "Effexor XR" on the cap and "37.5" on the body.

NDC 0008-0837-01, bottle of 100 capsules.

NDC 0008-0837-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

Bottles: Protect from light. Dispense in light-resistant container.

Blisters: Protect from light. Use blister carton to protect contents from light.

75 mg, peach cap and body with "w" and "Effexor XR" on the cap and "75" on the body.

NDC 0008-0833-01, bottle of 100 capsules.

NDC 0008-0833-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

150 mg, dark orange cap and body with "w" and "Effexor XR" on the cap and "150" on the body.

NDC 0008-0836-01, bottle of 100 capsules.

NDC 0008-0836-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

Manufactured by:
Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101

CI 5044-5 Revised April 14, 2000

Shown in Product Identification Guide, page 341

ENBREL®

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[ĕn' brĕl]

etanercept

DESCRIPTION

ENBREL (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 935 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

ENBREL is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration after reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol). Following reconstitution, the solution of ENBREL is clear and colorless, with a pH of 7.4 ± 0.3. Each single-use vial of ENBREL contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

LINICAL PHARMACOLOGY

eneral

anercept binds specifically to tumor necrosis factor (TNF) id blocks its interaction with cell surface TNF receptors. NF is a naturally occurring cytokine that is involved in rmal inflammatory and immune responses. It plays an portant role in the inflammatory processes of rheumatoid thritis (RA), polyarticular-course juvenile rheumatoid arritis (JRA) and the resulting joint pathology.[1,2] Elevated vels of TNF are found in the synovial fluid of RA patients.[3] vo distinct receptors for TNF (TNFRs), a 55 kilodalton otein (p55) and a 75 kilodalton protein (p75), exist natully as monomeric molecules on cell surfaces and in soluble rms.[4] Biological activity of TNF is dependent upon bind- g to either cell surface TNFR.

anercept is a dimeric soluble form of the p75 TNF recepr that can bind to two TNF molecules. It inhibits the acity of TNF in vitro and has been shown to affect several imal models of inflammation, including murine collagenduced arthritis.[5,6] Etanercept inhibits binding of both NFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface NFRs, rendering TNF biologically inactive.[6] Cells expressg transmembrane TNF that bind ENBREL are not lysed vitro in the presence or absence of complement.[6]

anercept can also modulate biological responses that are duced or regulated by TNF, including expression of adhem molecules responsible for leukocyte migration (i.e., E-lectin and to a lesser extent intercellular adhesion mole-le-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and rum levels of matrix metalloproteinase-3 (MMP-3 or romelysin).[6]

armacokinetics

ter administration of 25 mg of ENBREL by a single subtaneous (SC) injection to three patients with RA, a mean half-life of 115 hours (range 98 to 300 hours) was obrved with a clearance of 89 mL/hr (52 mL/hr/m^2). A maxum serum concentration (Cmax) of 1.2 mcg/mL (range 0.6 1.5 mcg/mL) and time to Cmax of 72 hours (range 48 to hours) was observed in these patients. After continued sing of RA patients (N = 25) with ENBREL for 6 months th 25 mg twice weekly, the median observed level was) mcg/mL (range 1.7 to 5.6 mcg/mL). Based on the avail-le data, individual patients may undergo a two- to five-d increase in serum levels with repeated dosing. Serum ncentrations in patients with RA have not been measured periods of dosing that exceed 6 months.

armacokinetic parameters were not different between an and women and did not vary with age in adult patients. formal pharmacokinetic studies have been conducted to amine the effects of renal or hepatic impairment or interions with methotrexate.

diatric patients with JRA (ages 4 to 17 years) were adinistered 0.4 mg/kg of ENBREL for up to 18 weeks. The erage serum concentration after repeated dosing was l mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Preliminary ta suggest that the clearance of ENBREL is reduced ghtly in children ages 4 to 8 years. Children <4 years of e have not been studied.

LINICAL STUDIES

ult Rheumatoid Arthritis

e safety and efficacy of ENBREL were assessed in two ndomized, double-blind, controlled studies. Study I evalted 234 patients with active RA who were ≥ 18 years old, d failed therapy with at least one but no more than four ease-modifying antirheumatic drugs (DMARDs; e.g., hyoxychloroquine, oral or injectable gold, methotrexate TX], azathioprine, D-penicillamine, sulfasalazine), and d ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR 28 mm/hour, CRP > 2.0 mg/dL, or morning stiffness for ≥ minutes. Doses of 10 mg or 25 mg ENBREL or placebo re administered SC twice a week for 6 consecutive nths. Results from patients receiving 25 mg are prested below.

udy II evaluated 89 patients with similar inclusion crite- to Study I except that subjects in Study II had additionly received MTX for at least 6 months with a stable dose 2.5 to 25 mg/wk) for at least 4 weeks and they had at least ender or painful joints. Subjects in Study II received a se of 25 mg ENBREL or placebo SC twice a week for 6 nths in addition to their stable MTX dose.

udy III compared the efficacy of ENBREL to MTX in pants with active RA. This study evaluated 632 patients o were ≥ 18 years old with early (≤ 3 years disease duion) active RA; had never received treatment with MTX; d had ≥ 12 tender joints, ≥ 10 swollen joints, and either ;R ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for 45 minutes. Doses of 10 mg or 25 mg ENBREL were administered SC twice a week for 12 consecutive months. Results from patients receiving 25 mg are presented below. TX tablets (escalated from 7.5 mg/week to a maximum of mg/week over the first 8 weeks of the trial) or placebo lets were given once a week on the same day as the intion of placebo or ENBREL doses, respectively.

e results of all 3 trials were expressed in percentage of tients with improvement in RA using American College of eumatology (ACR) response criteria.[7]

nical Response

e percent of ENBREL-treated patients receiving ACR 20, , and 70 responses was consistent across all 3 trials. The sults of the three trials are summarized in Table 1.

e table 1 above]

e time course for ACR 20 response rates for patients reving placebo or 25 mg ENBREL in Studies I and II is summarized in Figure 1. The time course of responses to ENBREL in Study III were similar.

Table 1
ACR Responses in Placebo- and Active-Controlled Trials
(Percent of Patients)

	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
Response	Placebo N = 80	ENBREL[a] N = 78	MTX/Placebo N = 30	MTX/ENBREL[a] N = 59	MTX N = 217	ENBREL[a] N = 207
ACR 20						
Month 3	23%	62%[b]	33%	66%[b]	56%	62%
Month 6	11%	59%[b]	27%	71%[b]	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%[b]	0%	42%[b]	24%	29%
Month 6	5%	40%[b]	3%	39%[b]	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%[b]	0	15%[b]	7%	13%[c]
Month 6	1%	15%[b]	0	15%[b]	14%	21%[c]
Month 12	NA	NA	NA	NA	22%	25%

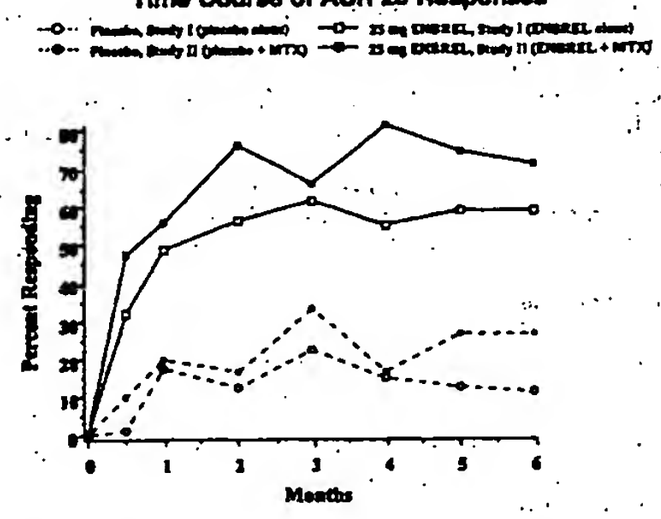
a. 25 mg ENBREL SC twice weekly.
b. $p < 0.01$, ENBREL vs. placebo.
c. $p < 0.05$, ENBREL vs. MTX.

Table 2
Components of ACR Response in Study I

	Placebo N = 80		ENBREL[a] N = 78	
Parameter (median)	Baseline	3 Months	Baseline	3 Months*
Number of tender joints[b]	34.0	29.5	31.2	10.0[f]
Number of swollen joints[c]	24.0	22.0	23.5	12.6[f]
Physician global assessment[d]	7.0	6.5	7.0	3.0[f]
Patient global assessment[d]	7.0	7.0	7.0	3.0[f]
Pain[d]	6.9	6.6	6.9	2.4[f]
Diability index[e]	1.7	1.8	1.6	1.0[f]
ESR (mm/hr)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

* Results at 6 months showed similar improvement.
a. 25 mg ENBREL SC twice weekly.
b. Scale 0-71.
c. Scale 0-68.
d. Visual analog scale; 0 = best, 10 = worst.
e. Health assessment questionnaire; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
f. $p < 0.01$, ENBREL vs. placebo, based on mean percent change from baseline.

Figure 1
Time Course of ACR 20 Responses



Among patients receiving ENBREL, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III; 25 mg ENBREL was more effective than 10 mg (10 mg was not evaluated in Study II). ENBREL was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, approximately 10% of patients treated with ENBREL achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. The results of the components of the ACR response criteria for Study I are shown in Table 2. Findings were similar in Studies II and III for patients treated with ENBREL.

[See table 2 above]

After discontinuation of ENBREL, symptoms of arthritis generally returned within a month. Reintroduction of treatment with ENBREL after discontinuations of up to 18 months resulted in the same magnitudes of response as patients who received ENBREL without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 36 months in open-label extension treatment trials when patients received ENBREL without interruption.

A Health Assessment Questionnaire (HAQ),[8] which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during Studies I and III. All subdomains of the HAQ were improved in patients treated with ENBREL.

In Study III, health outcome measures were assessed by the SF-36 questioinnaire. The eight subscales of the SF-36 were combined into two summary scales, the physical component summary (PCS) and the mental component sumary (MCS).[9] At 12 months, patients treated with 25 mg ENBREL showed significantly more improvement in the PCS compared to the 10 mg ENBREL group, but not in the MCS.

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in total Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were read at baseline, 6 months, and 12 months. The results are shown in Table 3. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

[See table 3 at top of next page]

Polyarticular-Course Juvenile Rheumatoid Arthritis (JRA)

The safety and efficacy of ENBREL were assessed in a two-part study of 69 children with polyarticular-course JRA who had a variety of JRA onset types. Patients ages 4 to 17 years with moderately to severely active polyarticular-course JRA refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) ENBREL SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on ENBREL or receive placebo for four months and assessed for disease flare. Responses were measured using the JRA Definition of Improvement (DOI),[10] defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a ≥ 30% worsening in three of six JRA core set criteria and ≥ 30% improvement in not more than one of six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.[11] In part 2, 6 of 25 (24%) patients remaining on ENBREL experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received ENBREL and 28 days for patients who received placebo. Each component of the JRA core set criteria worsened in the arm that

Continued on next page

el—Cont.

sived placebo and remained stable or improved in the m that continued on ENBREL. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on ENBREL continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JRA patients who developed a disease flare in part 2 and reintroduced ENBREL treatment up to 4 months after discontinuation re-responded to ENBREL therapy, in open-label studies. Most of the responding patients who continued ENBREL therapy without interruption have maintained responses for up to 18 months.

Studies have not been done in patients with polyarticular-course JRA to assess the effects of continued ENBREL therapy in patients who do not respond within 3 months of initiating ENBREL therapy, or to assess the combination of ENBREL with methotrexate.

Immunogenicity

Patients were tested at multiple timepoints for antibodies to ENBREL. Antibodies to ENBREL, all non-neutralizing, were detected at least once in sera of 16% of adult rheumatoid arthritis patients. No apparent correlation of antibody development to clinical response or adverse events was observed. Results from JRA patients were similar to those seen in adult RA patients treated with ENBREL. The long-term immunogenicity of ENBREL is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ENBREL in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENBREL with the incidence of antibodies to other products may be misleading.

INDICATIONS AND USAGE

ENBREL is indicated for reducing signs and symptoms and delaying structural damage in patients with moderately to severely active rheumatoid arthritis. ENBREL can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL is indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs.

CONTRAINDICATIONS

ENBREL should not be administered to patients with sepsis or with known hypersensitivity to ENBREL or any of its components.

WARNINGS

IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL. MANY OF THESE SERIOUS EVENTS HAVE OCCURRED IN PATIENTS WITH UNDERLYING DISEASES THAT IN ADDITION TO THEIR RHEUMATOID ARTHRITIS COULD PREDISPOSE THEM TO INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ENBREL SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ENBREL SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ENBREL SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS, INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ENBREL IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS, OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (see **PRECAUTIONS, ADVERSE REACTIONS, Infections**).

PRECAUTIONS

General

Allergic reactions associated with administration of ENBREL during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ENBREL should be discontinued immediately and appropriate therapy initiated.

Information to Patients

If a patient or caregiver is to self-administer ENBREL, he/she should be instructed in injection techniques and how to measure the correct dose to help ensure the proper administration of ENBREL (see **How to Use ENBREL, Instructions for Preparing and Giving an Injection.**) The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to self-inject subcutaneously should be assessed. A puncture-resistant container for disposal of needles and syringes should be used. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Immunosuppression

The possibility exists for anti-TNF therapies, including ENBREL, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections** and **Malignancies**). The safety and efficacy of ENBREL in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

No data are available on the effects of vaccination in patients receiving ENBREL. Live vaccines should not be given concurrently with ENBREL. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL (see **PRECAUTIONS, Immunosuppression**).

It is recommended that JRA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL therapy. Two JRA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoantibody Formation

Treatment with ENBREL may result in the formation of autoimmune antibodies (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions

Specific drug interactions studies have not been conducted with ENBREL.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

Pregnancy (Category B)

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to ENBREL. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether ENBREL is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ENBREL, a decision should be made whether to discontinue nursing or to discontinue the drug.

Geriatric Use

A total of 197 RA patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use

ENBREL is indicated for treatment of polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. For issues relevant to pediatric patients, in addition to other sections of the label, see also **PRECAUTIONS, Immunizations**, and **ADVERSE REACTIONS, Adverse Reactions in Pediatric Patients**. ENBREL has not been studied in children < 4 years of age.

ADVERSE REACTIONS

ENBREL has been studied in 1197 patients with RA, followed for up to 36 months. The proportion of patients who discontinued treatment due to adverse events was approximately 4% in both ENBREL and placebo-treated patients.

Injection Site Reactions

In controlled trials, 37% of patients treated with ENBREL developed injection site reactions. All injection site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given.

Infections

In controlled trials, there were no differences in rates of infection among patients treated with ENBREL and those treated with placebo or MTX. The most common type of infection was upper respiratory infection, which occurred in 16% of placebo-treated patients and 29% of patients treated with ENBREL. When the longer observation of patients on ENBREL was accounted for, the event rate was similar in both groups.

In placebo-controlled trials in DMARD-refractory RA, no increase in the incidence of serious infections was observed (approximately 1% in both placebo and ENBREL-treated groups). The rates of infections for the ENBREL arm in Study III were similar. In all clinical trials in RA, 50 of 1197 subjects exposed to ENBREL for up to 36 months experienced serious infections, including pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL. Some have occurred within a few weeks after initiating treatment with ENBREL. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. (See **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL treatment may increase mortality in patients with established sepsis.[12]

Malignancies

Seventeen malignancies of various types were observed in 1197 RA patients treated in clinical trials with ENBREL for up to 36 months. The observed rates and incidences were similar to those expected for the population studied.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple timepoints. In Studies I and II, the percentage of the patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with ENBREL (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti–double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with ENBREL compared to 4% of placebo-treated patients) and by crithidia lucilae assay (3% of patients treated with ENBREL compared to none of placebo-treated patients). The proportion of patients treated with ENBREL who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In Study III, no pattern of increased autoantibody development was seen in ENBREL patients compared to MTX patients.

No patients in placebo- and active-controlled trials developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with ENBREL on the development of autoimmune diseases is unknown.

Other Adverse Reactions

Table 4 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III.

[See table 4 at bottom of next page]

Among patients with rheumatoid arthritis treated in placebo-controlled trials, serious adverse events occurred at a frequency of 4% in 349 patients treated with ENBREL compared to 5% of 152 placebo-treated patients. In Study III, serious adverse events occurred at a frequency of 6% in 415 patients treated with ENBREL compared to 8% of 217 MTX-treated patients. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL, malignancies (see **ADVERSE REACTIONS, Malignancies**) and infections (see **ADVERSE REACTIONS, Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed included heart failure, myocardial infarction, myocardial ischemia, cerebral ischemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal hemorrhage, bursitis, depression, dyspnea, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, and thrombophlebitis.

Adverse Reactions in Pediatric Patients

In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

Severe adverse reactions reported in 69 JRA patients aged 4 to 17 years included varicella (see also **PRECAUTIONS, Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

Forty-three of 69 (62%) children with JRA experienced an infection while receiving ENBREL during 3 months of study (part 1 open-label), and the frequency and severity of infec-

Table 3
Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg Enbrel	MTX - ENBREL (95% Confidence Interval*)	P value
12 Months	Total Sharp score	1.59	1.00	0.59 (−0.12, 1.30)	0.110
	Erosion score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN score	0.56	0.52	0.04 (−0.39, 0.46)	0.529
6 Months	Total Sharp score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN score	0.38	0.27	0.11 (−0.14, 0.35)	0.585

* 95% confidence intervals for the differences in change scores between MTX and ENBREL

tions was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JRA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations.

The following adverse events were reported more commonly in 69 JRA patients receiving 3 months of ENBREL compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 events per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

OVERDOSAGE

The maximum tolerated dose of ENBREL has not been established in humans. Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of ENBREL. Single IV doses up to 60 mg/m^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities. The highest dose level evaluated in RA patients has been a single IV loading dose of 32 mg/m^2 followed by SC doses of 16 mg/m^2 (~25 mg) administered twice weekly. In one RA trial, one patient mistakenly self-administered 62 mg ENBREL SC twice weekly for 3 weeks without experiencing adverse effects.

DOSAGE AND ADMINISTRATION

The recommended dose of ENBREL for adult patients with rheumatoid arthritis is 25 mg given twice weekly as a subcutaneous injection 72–96 hours apart (see **Clinical Studies**). Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL. Higher doses of ENBREL have not been studied.

The recommended dose of ENBREL for pediatric patients ages 4 to 17 years with active polyarticular-course JRA is 0.4 mg/kg (up to a maximum 25 mg per dose) given twice weekly as a subcutaneous injection 72–96 hours apart. Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL. Concurrent use with methotrexate and higher doses of ENBREL have not been studied in pediatric patients.

Preparation of ENBREL

ENBREL is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in how to measure the correct dose and in injection technique.

Note: The needle cover of the diluent syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

ENBREL should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of ENBREL. During reconstitution of ENBREL, the diluent should be injected very slowly into the vial. Some foaming will occur. This is normal. To avoid excessive foaming, **do not shake or vigorously agitate**. The contents should be swirled gently during dissolution. Generally, dissolution of ENBREL takes less than 10 minutes. The reconstituted solution should be clear and colorless and used within 6 hours (see **Storage and Stability**).

Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains. Withdraw the solution into the syringe, removing only the dose to be given from the vial. Some foam or bubbles may remain in the vial.

No other medications should be added to solutions containing ENBREL, and do not reconstitute ENBREL with other diluents. Do not filter reconstituted solution during preparation or administration.

Rotate sites for self-injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red, or hard. (See **How to Use ENBREL, Instructions for Preparing and Giving an Injection** instruction sheet.)

Storage and Stability

Do not use a dose tray beyond the date stamped on the carton dose tray label, vial label, or diluent syringe label. The dose tray containing ENBREL (sterile powder) must be refrigerated at 2–8°C (36–46°F). DO NOT FREEZE.

Administer reconstituted solutions as soon as possible after reconstitution. If not administered immediately after reconstitution, ENBREL may be stored in the vial at 2–8°C (36–46°F) for up to 6 hours. **ANY ENBREL NOT USED WITHIN 6 HOURS OF RECONSTITUTION SHOULD BE DISCARDED. PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED.**

HOW SUPPLIED

ENBREL is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg single-use vial of etanercept, one syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one plunger, and two alcohol swabs.

Rx only

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Table 4
Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials*

	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
Event	Placebo† (n = 152)	ENBREL (n = 349)	MTX (n = 217)	ENBREL (n = 415)
Injection site reaction	10	37	7	34
Infection	32	35	72	64
Non-upper respiratory infection**	32	38	60	51
Upper respiratory infection**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal Pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	-	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis ("MTX lung")	-	-	2	0

* Includes data from the 6-month study in which patients received concurrent MTX therapy.
† The duration of exposure for patients receiving placebo was less than the ENBREL-treated patients.
** Includes data from two of the three placebo controlled trials.

EQUAGESIC® ℞

[ek 'wa-je 'zik]
(meprobamate with aspirin)

DESCRIPTION

Each tablet of Equagesic contains 200 mg meprobamate and 325 mg aspirin. The inactive ingredients present are cellulose, D&C Yellow 10, FD&C Red 3, FD&C Yellow 6, hydrogenated vegetable oil, magnesium stearate, polacrilin potassium, and starch.

HOW SUPPLIED

Equagesic® (meprobamate with aspirin) Tablets, 200 mg meprobamate and 325 mg aspirin, are available as follows: NDC 0008-0091, pink and yellow, double-layer, round, scored tablet marked "WYETH" and "91", in bottles of 100 tablets.

Store at room temperature, approx. 25°C (77°F).
Keep tightly closed.
Protect from light.
Dispense in light-resistant, tight container.

The appearance of EQUAGESIC tablets is a registered trademark of Wyeth-Ayerst Laboratories.

Manufactured by:
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101
CI 3343-6 Revised November 18, 1994

For full prescribing information write to Professional Service, Wyeth-Ayerst Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101, or contact your local Wyeth-Ayerst representative.

EQUANIL® ℞

[ek 'wah-nil]
(meprobamate)
Tablets

DESCRIPTION

Meprobamate is a white powder with a characteristic odor and a bitter taste. It is slightly soluble in water, freely soluble in acetone and alcohol, and sparingly soluble in ether. Equanil tablets contain 200 mg or 400 mg meprobamate. The inactive ingredients present are lactose, methylcellulose, polacrilin potassium, and stearic acid.

HOW SUPPLIED

Equanil® (meprobamate) Tablets are available in the following dosage strengths:
200 mg, NDC 0008-0002, white, five-sided tablet marked "WYETH" and "2", in bottles of 100 tablets.
400 mg, NDC 0008-0001, white, round, scored tablet marked "WYETH" and "1", in bottles of 100 and 500 tablets.

Keep tightly closed.
Dispense in tight container.
Store at room temperature, approximately 25°C (77°F).

Manufactured by:
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101
CI 3313-6 Revised January 18, 1994

For prescribing information write to Professional Service, Wyeth-Ayerst Pharmaceuticals, P.O. Box 8299, Philadelphia, PA 19101, or contact your local Wyeth-Ayerst representative.

FACTREL® ℞

[făc-trĕl ']
(gonadorelin hydrochloride)
Synthetic Luteinizing Hormone Releasing Hormone (LH-RH)
DIAGNOSTIC USE ONLY

HOW SUPPLIED

LYOPHILIZED POWDER
in single-dose Secule® vials containing 100 mcg (NDC 0046-0507-05) and 500 mcg (NDC 0046-0509-05) gonadorelin as

Continued on next page